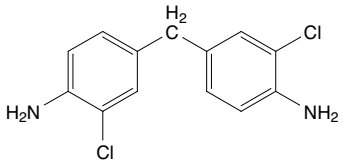
4,4′-Methylenedianiline and Its Dihydrochloride

CAS Nos. 101-77-9 and 13552-44-8

Reasonably anticipated to be human carcinogens

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

4,4′-Methylenedianiline and its dihydrochloride salt are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 4,4′-methylenedianiline dihydrochloride caused tumors at several different tissue sites in mice and rats. Administration of 4,4′-methylenedianiline dihydrochloride in the drinking water caused benign and/or malignant tumors of the thyroid gland (C-cell adenoma or follicular-cell adenoma or carcinoma) in mice and rats of both sexes and benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in mice of both sexes and in male rats. It also caused malignant lymphoma in female mice and benign adrenal-gland tumors (pheochromocytoma) in male mice (NTP 1983).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 4,4′-methylenedianiline or its dihydrochloride.

Properties

4,4′-Methylenedianiline is an aromatic amine that exists at room temperature as colorless to pale yellow to tan flakes or lumps with a faint amine-like odor (IARC 1986, Akron 2009, HSDB 2009). 4,4′-Methylenedianiline is only slightly soluble in water, but soluble in ethanol, benzene, diethyl ether, and acetone. The dihydrochloride salt is soluble in water. 4,4′-Methylenedianiline is stable at normal temperatures and pressures (Akron 2009). Physical and chemical properties of 4,4′-methylenedianiline are listed in the following table.

Property	Information
Molecular weight	198.3[a]
Specific gravity	1.056 at 100°C/4°C[a]
Melting point	91.5°C to 92°C[a]
Boiling point	398°C to 399°C at 768 mm Hg[a]
Log K_{ow}	1.59[a]
Water solubility	1 g/L at 25°C[b]
Vapor pressure	1 mm Hg at 197°C[a]
Vapor density relative to air	6.8[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

More than 90% of the 4,4′-methylenedianiline produced in the United States is used as a chemical intermediate in the closed-system production of 4,4′-methylenedianiline diisocyanate and polyisocyanates (NTP 1983, IARC 1986). These products are used to produce a variety of polymers and resins, such as polyurethane foam, elastomers (e.g., Spandex fibers), and isocyanate resins. 4,4′-Methylenedianiline is also used as a cross-linking agent for epoxy resins, and the U.S. Food and Drug Administration has approved the use of these epoxy resins to coat containers for beverages having an alcohol content of up to 8%. 4,4′-Methylenedianiline is also used as an analytical reagent for analysis, including the determination of tungsten and sulfates, as a corrosion inhibitor, as an antioxidant and curative agent in rubber, and to prepare azo dyes (IARC 1986, ATSDR 1998). No data were available on the use of the dihydrochloride salt.

Production

4,4′-Methylenedianiline has been produced commercially in the United States since the early 1920s (IARC 1986). It is available in bulk quantities containing approximately 96% 4,4′-methylenedianiline, 3% other isomeric amines, and traces of aniline (ATSDR 1998). In the early 1980s, six or seven manufacturers produced between 200 million and 400 million pounds of 4,4′-methylenedianiline per year. In 1987, about 600 million pounds was produced and used captively as a chemical intermediate, 4.5 million pounds was produced domestically for sale, and 1.8 million pounds was imported (OSHA 1987). In 2009, 4,4′-methylenedianiline was produced by ten manufacturers worldwide, including one in the United States (SRI 2009), and was available from 28 suppliers, including 14 U.S. suppliers (ChemSources 2009). No producers or suppliers of the hydrochloride salt were identified. From 1989 to 1993, U.S. imports of 4,4′-methylenedianiline were 3.3, 2.9, 2.4, 2.0, and 1.1 million pounds, and U.S. exports were 28.9, 29.8, 12.8, 15.7, and 9.9 million pounds (ATSDR 1998). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 4,4′ methylenedianiline totaled 100 million to 500 million pounds in 1986, falling to between 1 million and 10 million pounds in 1990, remaining in that range in through 2002 (EPA 2004), and returning to between 100 million and 500 million pounds in 2006 (EPA 2009). No data on U.S. production, imports, or exports of the dihydrochloride salt were found.

Exposure

Although most exposure to 4,4′ methylenedianiline is occupational, the general population may be exposed through dermal contact with trace amounts present in consumer products made from polyurethane foam, Spandex, and epoxy-containing products. Although 4,4′-methylenedianiline may be used in their production, very little of the chemical is present in its free state in the final products. Levels of 4,4′-methylenedianiline in food and food packaging are so low that exposure is unlikely. Polyurethane is used in medical devices, and exposure may occur from small releases of 4,4′-methylenedianiline during sterilization with gamma radiation; patients most likely to be exposed from this source are those receiving frequent blood transfusions or undergoing kidney dialysis (ATSDR 1998).

4,4′-Methylenedianiline may be released to the environment during industrial production and use (IARC 1986, ATSDR 1998). Very few data were available regarding concentrations of 4,4′-methylenedianiline in ambient air, surface water, industrial effluents, or soil. According to EPA's Toxics Release Inventory, environmental releases of 4,4′-methylenedianiline declined from 736,000 lb in 1988 to 29,000 lb in 1992 and remained between 29,000 and 78,000 lb through 2003. Releases increased in 2004, reaching 207,176 lb in 2005, and then decreased, reaching 67,423 lb in 2007. In 2007, 58,000 lb of 4,4′-methylenedianiline was released from one facility to an underground injection well, and most of the remainder was released to air. Reporting is not required for the hydrochloride salt (TRI 2009). If 4,4′-methylenedianiline is released to air, the vapor phase will be degraded by photochemically produced hydroxyl radicals, with a

half-life of 1.6 hours (HSDB 2009). If released to soil, 4,4′-methylenedianiline will covalently bind to humic material, but will leach from soil without humic material. If released to water, 4,4′-methylenedianiline may covalently bind to suspended solids and sediments containing humic material. On the water surface, it will be susceptible to degradation by photochemically produced hydroxyl and peroxy radicals, with a half-life of 19 to 30 hours.

The primary routes of potential occupational exposure to 4,4′-methylenedianiline are inhalation and dermal contact. Workers may be exposed while producing, formulating, and packaging the chemical, during its use, and from hydrolysis of 4,4′-methylenediphenyl diisocyanate. No 4,4′-methylenedianiline is released during autoclave sterilization of medical equipment (IARC 1986, ATSDR 1998). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that over 15,000 workers, including about 3,400 women, potentially were exposed to 4,4′-methylenedianiline (NIOSH 1990). In 1992, the Occupational Safety and Health Administration estimated that 3,836 workers in 11 principal industry sectors were exposed to 4,4′-methylenedianiline (OSHA 1992), at air concentrations ranging from 1 to 250 ppb and for average annual exposure durations of 47 to 250 days. 4,4′-Methylenedianiline was measured at concentrations of up to 31 mg/m^3 in air inside facilities where it was produced and up to 1.6 mg/m^3 inside fabrication facilities while it was being used. It was detected in the urine of 4 of 27 production workers (14.9%) at concentrations of at least 200 µg/L in 1970, but in the urine of only 0.09% of workers (numbers not reported) at concentrations of 20 µg/L or less in 1980 (IARC 1986, ATSDR 1998). In a 2005 risk assessment, the concentration of 4,4′-methylenedianiline in freshly produced polyurethane foam was 2 to 3.5 mg/kg at the time of demolding, declining to 1 mg/kg one hour after demolding and continuing to decline slowly over time (Lewandowski *et al.* 2005); based on these concentrations, cancer risks from dermal exposure were found to be below the level of concern. It was assumed that adequate ventilation would minimize inhalation exposure.

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: 4,4′-Methylenedianiline is listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of 4,4′-methylenedianiline is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb for 4,4′-methylenedianiline.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: 4,4′-Methylenedianiline is a listed substance subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.010 ppm for 4,4′-methylenedianiline.

Short-term exposure limit (STEL) = 0.10 ppm for 4,4′-methylenedianiline.

Comprehensive standards have been developed for occupational exposure to 4,4′-methylenedianiline and its salts.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.1 ppm for 4,4′-methylenedianiline.

National Institute for Occupational Safety and Health (NIOSH)

4,4′-Methylenedianiline is listed as a potential occupational carcinogen.

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